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Pharmacokinetics and Pharmacodynamics in Space

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WORKSHOP PARTICIPANTS

Co-Chairs

Nitza M. Cintrón, Ph.D.
Chief, Biomedical Operations
and Research Branch
NASA - Johnson Space Center

Stuart Feldman, Ph.D.
Professor of Pharmaceutics
University of Houston

Panelists

Gordon Amidon, Ph.D.
Professor of Pharmaceutics
University of Michigan
Pharmaceutics; drug delivery systems

Leslie Z. Benet, Ph.D.
Professor of Pharmacy
University of California
Pharmacokinetics and biopharmaceutics

Jerry Collins, Ph.D.
Pharmacologist
National Institutes of Health
Food and Drug Administration
Applied pharmacology and drug development

Gerhard Levy, Ph.D.
Director, Clinical Pharmacokinetics
Research Center
State University of New York at Buffalo
*Bioavailability, pharmacodynamics,
and disease states*

Grant R. Wilkinson, Ph.D.
Professor of Pharmacology
Vanderbilt University
Physiological factors in pharmacokinetics

Melvin E. Andersen, Ph.D.
Acting Director, Toxic Hazards Division
Wright-Patterson Air Force Base
*Physiological and pharmacokinetic models;
applications in toxicology
(absent at the workshop)*

Conference Organizer

Lakshmi Putcha, Ph.D.
Biomedical Operations and Research Branch
NASA - Johnson Space Center

Participants

John B. Charles, Ph.D.
Space Biomedical Research Center
NASA - Johnson Space Center

Joan Vernikos Danellis, Ph.D.
Office of the Director of Space Research
Ames Research Center

Joseph Dardano
General Electric Government Services
Johnson Space Center

G. Wyckliffe Hoffler, M.D.
Biomedical Operations and Research Office
Kennedy Space Center

Charles W. Lloyd, Ph.D.
KRUG International
Johnson Space Center

WORKSHOP AGENDA

Monday, August 29, 1988

8:30 a.m.	Welcome	Dr. Carolyn L. Huntoon
8:45 a.m.	Space Station Program	
	-General Design -Environmental Health -Health Maintenance Facility	Mr. Gary H. Kitmacher Dr. Dane Russo Dr. Charles W. Lloyd
10:15 a.m.	Break	
10:30 a.m.	Space Physiology and Medicine	
	-Physiological Adjustments and Pharmacokinetic Deviations in Microgravity	Dr. Nitza M. Cintrón
11:30 a.m.	Scope of the Workshop	Dr. Stuart Feldman
12:00 p.m.	Lunch	
12:45 p.m.	Panel Discussions	
	-Physiological Variables -Pharmacokinetic Consequences -Pharmacodynamic Implications	
4:45 p.m.	End of Session	
5:30 p.m.	Social Hour	
6:30 p.m.	Dinner	

Tuesday, August 30, 1988

8:00 a.m.	Summary of Previous Discussions	Dr. Lakshmi Putcha
8:15 a.m.	Panel Discussions	
	-Biopharmaceutics	
	-Drug Monitoring Methods	
	-Data Collection and Analysis Methods	
10:30 a.m.	Break	
10:45 a.m.	Special Methods of Evaluation	
	-Ground-Based Simulation Models	
	-Physiological-Pharmacokinetic Modeling	
11:45 a.m.	Special Areas of Interest	
	-Mission-Specific Issues	
	-Summary	
12:30 p.m.	Lunch	
1:00 p.m.	Johnson Space Center Tour	

FOREWORD

Space flight incorporates unique environmental factors to which organisms have not been exposed in the course of their phylogenetic development. Any observed physiological response in the normal astronaut population is actually the result of the combination or integration of the responses from several different body systems, each responding simultaneously to the challenges of space flight and weightlessness. Some of the major physiological changes induced by weightlessness are fluid shifts, electrolyte balance changes, and hormonal and metabolic changes, including carbohydrate, protein, and fat utilization. While it is apparent that space flight incurs marked physiological changes, the effect of these changes on other physiology-dependent dynamic processes like the pharmacokinetics and pharmacodynamics of therapeutic agents is not clearly understood.

Pharmacological intervention to control pathophysiologic disorders occurring during space flight will likely increase with the advent of extended duration missions on the Space Shuttle and on Space Station *Freedom*. In order to ensure safe and effective therapeutic intervention in space, it is important to understand the clinical pharmacology of medications administered to crewmembers during missions. The issue of altered response to drugs in space was raised as early as the pre-Skylab era, but has not been pursued actively due to the lack of adequate analytical techniques, as well as technical feasibility during flight. Although efforts to identify effective treatment methods for space motion sickness (SMS) during the shuttle program have reactivated interest in pharmacokinetics and pharmacodynamics in space, application of research findings in this area goes well beyond the treatment of SMS.

The biological effect elicited by a therapeutic agent in a given dosage form under any conditions is a function of the intrinsic activity of the agent and its concentration at the site of action. The onset, intensity, and duration of the pharmacological response produced by drugs, collectively known as the pharmacodynamics of an administered medication, depend upon the processes that characterize their absorption, distribution, metabolism, and elimination. The mathematical description of these processes and their interrelationships are described by pharmacokinetics. Knowledge of the kinetics and dynamics of a pharmacological agent allows (1) the design and development of an effective dosage

regimen; (2) readjustment of that regimen to individual requirements; and (3) an understanding of unusual pharmacological responses, with correction as needed.

The four parameters of drug pharmacokinetics are: (1) *elimination half-life*, the time required for a given agent to decrease to one half of its initial concentration; (2) *volume of distribution*, a proportionality constant that describes the total amount of drug in the body relative to its plasma concentration; (3) *bioavailability*, the measurement of both the relative amount of an administered dose that reaches the general circulation and the rate at which this occurs; and (4) *clearance*, the virtual volume of blood or plasma cleared of drug by all applicable organs of elimination per unit time. These pharmacokinetic parameters are subject to variation due to a large number of biochemical, biological, and clinical factors such as gastrointestinal, hepatic, and renal function of the subject, body weight and size, disease state, and interaction with simultaneously administered drugs. A list of physiological factors that affect the pharmacokinetics of drugs are presented in Table 1.

Table 1. Primary Pharmacokinetic Variables Dependent Upon Physiological Variables

Primary Pharmacokinetic Parameter	Independent Physiological Variables
Absorption rate constant	Blood flow rate at absorption site Gastric emptying rate Gastrointestinal motility
Hepatic clearance	Hepatic blood flow Binding in blood Intrinsic hepatocellular activity (V_{max} K_{max})
Renal clearance	Renal blood flow Binding in blood Active secretion Active reabsorption Urine pH Urine flow
Volume of distribution	Binding in blood Binding in tissue Body composition Body size

Microgravity is known to induce changes in cardiovascular, renal, and hepatic function; microgravity can therefore be inferred to influence drug pharmacokinetics and pharmacodynamics. Indeed, preliminary findings with two drugs suggest that pharmacokinetics are altered by exposure to microgravity. Understanding the

pharmacokinetic behavior of medications administered in microgravity, and thereby allowing means with which to predict that behavior, however, requires the definition and understanding of the physiological mechanisms underlying these changes, and the sequence in which they occur. The most important aspect of pharmacokinetics in space medicine is that the pharmacokinetics of a drug govern the onset, intensity, and duration of the therapeutic activity of that drug. Furthermore, the magnitude of pharmacodynamic deviations as a result of pharmacokinetic changes may be different for different drugs, depending upon their intrinsic activity and structure-activity relationship. Therefore, the pharmacodynamics of drugs that are functionally and operationally crucial for a successful mission must be clearly understood in order to ensure safe and effective therapeutic intervention in space.

The Biomedical Operations and Research Branch at the Lyndon B. Johnson Space Center has been mandated with evaluating the pharmacokinetic and pharmacodynamic consequences of space flight and with making appropriate recommendations concerning effective modes of administration during space flight. As a first step in fulfilling this task, preliminary ground-based and inflight investigations have been conducted with acetaminophen, a well-characterized pain reliever, and scopolamine, which is in operational use as an antimotion-sickness agent. Results from these initial investigations confirm that space flight does induce significant changes in the absorption and bioavailability of these drugs after oral administration. These preliminary results, coupled with the extension of space flight duration in preparation for long-term missions onboard Space Station *Freedom*, prompted convening this workshop in order to discuss the physiological and pharmacological consequences of space flight with leading experts in the scientific community. Participants in the workshop are listed in the Appendix.

This document is a summation of presentations and discussions held at this workshop. The first section outlines the objectives and scope of the workshop, as presented to the participants, and offers a brief overview of workshop activities. The second section consists of panelists' comments. The third and final section provides a summary of recommendations.

L. Putcha, Ph.D.

Pharmacologist

Biomedical Operations and Research Branch

WORKSHOP OBJECTIVES

This workshop was organized and conducted to identify and discuss some of the major issues of pharmacokinetics and pharmacodynamics in space medicine and seek recommendations for research and operations from leading scientists in the field. The specific objectives of the workshop were to accomplish the following:

1. Present issues and concerns of pharmacokinetics and pharmacodynamics in space medicine
2. Solicit assistance in predicting alterations in the pharmacokinetics and pharmacodynamics of drugs in microgravity
3. Identify and prioritize research objectives and operational strategies for safe and effective drug treatment in space
4. Initiate collaborative research endeavors with outside institutions
5. Establish ongoing consulting relationships with leading experts in the field
6. Prepare a reference document that defines the direction of future research and operational issues in clinical pharmacology during space flight

WORKSHOP SCOPE

The following specific topics were presented for discussion. The issues listed under each of these topics were addressed in separate sessions.

Effect of Physiologic Variables on Pharmacokinetic Parameters

- ~ What are the important physiologic parameters that may affect drug pharmacokinetics in microgravity?
- ~ Does altered gastrointestinal motility affect gastrointestinal absorption?
- ~ Will bioavailability of medications differ in space?
- ~ Does drug distribution change in microgravity?
- ~ Does microgravity affect drug metabolism?

Biopharmaceutical Aspects of Space Medicine

- ~ What kinds of dosage forms should be considered?
 - Do conventional formulations work?
 - Are specialized delivery systems feasible?
 - What are the optimum methods of delivery?
- ~ What kinds of dosage regimens may be recommended?

Pharmacodynamics Issues of Clinical Importance

- ~ Will microgravity change dose-response relationships?
- ~ Are there specific drugs that may be more sensitive to pharmacodynamic changes?
- ~ Will microgravity affect the therapeutic index of operationally crucial medications?

Methodological Issues

- ~ What methods of drug monitoring are suitable for application on the ground and in flight?
- ~ Which methods of sample handling and analysis are suitable for space flight?
- ~ What kind of modifications to conventional research protocols are necessary in order to gather the best possible data?

Special Areas of Concern

- ~ What flight-specific changes can be expected and how can they be identified?
- ~ Which ground-based simulation models are suitable for pharmacokinetic investigations?
- ~ Can physiologically based pharmacokinetic and pharmacodynamic models be developed to identify flight-induced changes?
- ~ Can these models provide information on future research directions and choice of medications in space?

WORKSHOP OVERVIEW

The two-day conference began with opening remarks from Dr. Carolyn Huntoon, Director of Life Sciences at Johnson Space Center. The first session was devoted to a brief overview of ongoing programs in space medicine, including applicable Space Station subsystems, operational and research approaches to understanding the physiological effects of space flight, and preliminary findings on pharmacokinetic deviations in flight. The remainder of the conference was devoted to discussion of issues and recommendations for research and operations programs. Each issue listed in the previous section (Workshop Scope) was introduced by a predesignated panel member, and then opened for discussion. A synopsis of the discussion, including the panel's recommendations for research, was presented at the end of the symposium.

PANELISTS' COMMENTS

Physiological Considerations of Pharmacokinetic Parameters (Grant R. Wilkinson)

Drug concentrations within the body reflect the net balance between delivery/absorption, distribution, and elimination. The independent pharmacokinetic parameters volume of distribution and clearance quantify the distribution and elimination, respectively, of a drug in the body. These pharmacokinetic parameters are governed by physiologic factors such as organ size, relative binding characteristics between plasma and tissue proteins, and organ blood flow affecting volume of distribution of a drug; organ clearance has also been recognized as a function of blood flow, plasma binding and the intrinsic metabolic and/or excretion activity of the organ. Since zero gravity is known to affect physiological determinants such as cardiac output and organ blood flow, it is quite likely that a drug's pharmacokinetics will be different in space relative to earth. Whether these alterations are of sufficient magnitude to affect drug disposition significantly and produce a clinically significant change in the resulting pharmacological effects (efficacy and toxicity) can be answered only after assessing individual physiological and pharmacokinetic changes during space flight.

A drug's availability on space missions will be determined largely by preflight predictions of which medical or surgical situations are likely to occur. Since evaluation of clinical pharmacology in space is not feasible, predictions will be made based upon information collected on earth. For example, where alternative and equivalent medications are available for the same condition, prudence dictates selection of the drug with the widest therapeutic margin. These choices may be further refined by knowledge of the effects of microgravity upon critical determinants of the drug's disposition. For example, if kidney function is significantly impaired in space, then renal excretion of drugs and metabolites would be reduced. Thus, drugs that are eliminated chiefly via urinary excretion must be administered cautiously, with either modification of dosage in order to account for reduced renal function, or replaced by another agent that does not depend upon urinary excretion. Obviously, this approach requires knowledge of how zero gravity affects the physiological determinants of disposition, and an understanding of the relative importance of these physiological determinants in a drug's pharmacokinetics. Evaluation of candidate drugs

must include assessments of (1) the role of renal and/or hepatic function in elimination; (2) the role of plasma binding in distribution and/or elimination; and (3) the possibility that modest impairment of hepatic elimination may produce a significant oral-dose "first-pass" effect.

It is well known that any measured pharmacokinetic parameter is the result of interactions among physiological factors, such as drug-metabolizing enzymes and transport processes, and properties of a specific drug, such as binding to plasma and tissue proteins. It is unlikely that microgravity changes a drug's thermodynamic properties relative to 1 g. More likely, any pharmacokinetic changes in space would result from biological changes such as alterations in protein or enzyme levels. Accordingly, space-related alterations in disposition could be predicted with knowledge of how microgravity affects physiological determinants. This physiological modeling approach has been used successfully in the laboratory where perturbations have occurred in the determinants.

Sufficient information is not currently available for physiologic modeling. Animal studies may prove useful; comparison of the few microgravity data available with results from simulated model systems is also necessary. This process is not unlike evaluation of a new candidate drug for use in humans. The goals in both approaches cannot be precise prediction, but rather an assessment of likelihood that a given regimen will provide an acceptable level of risk-benefit.

Rapid and efficient collection of the necessary physiological information can be achieved using the following experimental approaches:

Renal function. The renal excretion of all drugs is in almost all instances proportional to the glomerular filtration rate (GFR). Accordingly, data on the extent of any change in this function under simulated zero-gravity conditions would be broadly applicable. If significant impairment is present, then dosages could be modified according to pharmacokinetically based procedures established and validated in patients with compromised kidney function. Since zero gravity is known to alter muscle mass, an absolute measure of GFR should be

used, rather than one based on creatinine clearance. Also, since the techniques are fairly simple, consideration should be given to obtaining this information in astronauts under zero gravity.

Drug-metabolizing enzyme activities. The biotransformation of a drug involves many enzymes and isozymes. It is impossible to evaluate the effects of zero gravity on every enzyme and isozyme with respect to the metabolism of a large number of specific drugs, particularly in vivo. The most practical approach appears to be an assessment of the magnitude of any changes in selected metabolic pathways in vitro. Thus, rats would be exposed to simulated or zero gravity, sacrificed and the liver removed in order to prepare a suitable in vitro metabolizing system (9000 g supernate, microsomes, etc.) for further study at 1 g. Reactions to be screened would use a variety of conventional substrates that are oxidized by the monooxygenase system(s), glucuronidation, sulfation, and acetylation. An alternative, perhaps more feasible approach that has direct applicability to evaluating changes in drug-metabolizing activity in astronauts during space flight would be to use probe drugs to elucidate the activity of specific enzymes. Techniques exist to allow ready noninvasive measurement of enzyme activity, especially monooxygenation, by analyzing a single timed urine sample after oral drug administration. Comparing enzyme activity in 1-g to that in true or simulated zero gravity would allow evaluation of the effect of space flight on metabolizing activity. Zero gravity may have only modest effects on metabolism; however, the potential for major changes must be assessed. If zero gravity induces a selective effect, such as impaired oxidation without affecting conjugation, then alternative medications may be indicated for use in space (e.g., substituting oxazepam for diazepam).

Cardiac output and organ blood flow. Drug distribution and delivery to the organs of elimination is dependent upon blood flow, and thus depends upon cardiac output. A simple, direct study of the effects of space flight on these cardiovascular parameters would involve injecting rats in flight with a bolus of radiolabelled microspheres. After a short (15 min) single blood-sampling period, the animals would be sacrificed and various tissues analyzed after return to Earth.

Organ size. Fluid redistribution is a well-described effect of microgravity. Fluid

redistribution leads to changes in organ size, which in turn could affect drug distribution. Information could be obtained from the preceding microsphere study on alterations in organ weights. (It may be important to evaluate the effect of increasing length of time in microgravity on organ weight, with the caveat that the adaptation period for animals is probably different than that for humans). After data collection, physiological modeling can be applied in which simulations using drugs with critical pharmacokinetic characteristics could then be performed and an assessment of integrated effects of individual changes made. Finally, an in vivo validation of the predicted pharmacokinetics in zero gravity may be required.

In each experimental approach, of paramount importance is assessment of the magnitude of change in zero gravity, and evaluation of whether a change is large enough to cause significant changes in drug disposition and effects. While large interindividual differences in pharmacokinetics exist at 1 g, this generally has little effect on successful clinical use of the drug. If such variability is 4- to 10-fold, a not unusual range for drug metabolizing activity, one must bear in mind that a statistically significant 30% change induced in microgravity may not ultimately affect clinical efficacy.

The focus of this section has been limited to the pharmacokinetic aspects of drug effects. Pharmacodynamics are also of critical importance, and must be rigorously addressed. In fact, it may be that pharmacodynamics, in combination with drug delivery, are primarily responsible for altered clinical responsiveness in zero gravity. Of particular concern in this respect are drugs that elicit their effects by way of homeostatic mechanisms. Set points within the cardiovascular-renal systems are known to be altered by zero gravity, as well as down- and up-regulation of certain physiological receptors. It would be surprising if these adaptations did not alter drug responsiveness.

Pharmacokinetic Considerations of Space Flight (Leslie Z. Benet)

Primary concern should be directed to the four major pharmacokinetic variables that can be used to evaluate drug kinetics. That is, clearance, a measure of the body's ability to eliminate a drug; volume of distribution, the space available in the body into which the drug may distribute; half-life, a dependent variable that changes inversely with clearance and directly with volume of distribution, but is useful as a measure of the appropriate dosing interval for drugs; and bioavailability, a measure of both the rate and extent by which drugs are made available to the systemic circulation following dose administration. All of these parameters could potentially change in space. Preliminary studies with acetaminophen and scopolamine have demonstrated that rates and possibly extent of absorption may vary when the saliva concentration profiles of these drugs are compared with preflight profiles. Rate of availability may be the most variable parameter noted in space, since gastrointestinal transit time and absorption of some drugs is known to change markedly depending on body position.

Few of the physiologic changes associated with short-term and long-term space flight allow quantitative prediction of changes in the other three primary pharmacokinetic parameters, clearance, volume of distribution, and half-life. Decreased urine volume early in flight and decreased uric acid excretion may indicate a reduced ability to pass drugs into the urine, resulting in decreased drug renal clearance. The stress related to space flight could result in increases in α -1-acid glycoprotein, which could result in increased protein binding of basic drugs, which could in turn produce decreased volume of distribution and clearance for such compounds. The increase in stroke volume, cardiac output, and heart rate, as well as the marked decrease noted in leg blood flow in flight, suggests that blood flow to various regions of the body may be altered; thus high-extraction ratio drugs may be expected to show an increase in clearance in flight corresponding to increased blood flow, when this is a rate-limiting factor.

Body composition changes during the first month in flight (losses of water, protein and fat) could lead to distribution changes; however, without further information concerning the relative changes in these three basic body components, it is difficult to predict whether significant changes would occur. Since there are no good non-drug markers for subjects not

in flight, the physiologic parameters measured are not expected to be predictive of changes in drug metabolism; therefore it is difficult to predict whether metabolic processes change in flight.

At this point, very little information is available about the pharmacokinetics of drugs in space, except for the high variability in rates of drug absorption. It is unclear from the data presented whether even the extent of absorption changes markedly. A number of well-designed studies are required before important questions can be answered concerning the possibility of marked change in drug kinetics leading to differences in pharmacodynamics which could ultimately result in reduced efficacy or other adverse effects.

Drug Absorption in Microgravity (Gordon L. Amidon)

Preliminary studies of salivary drug-concentration time curves in space indicate that the absorption of acetaminophen and scopolamine is highly variable in microgravity. The extent of drug absorption depends upon intestinal membrane permeability and gastrointestinal transit time; a drug's systemic availability also depends upon first-pass metabolism in the gastrointestinal tract and liver. The kinetics of drug absorption depend upon rate of gastric emptying (particularly for drugs with high intestinal-membrane permeability such as acetaminophen or scopolamine), varying intestinal-membrane permeability at different locations along the GI tract, and overall gastrointestinal transit time. In addition, the kinetics of drug metabolism by the liver will determine whether systemic availability of a particular drug is dose-rate dependent. All of these parameters can change in microgravity. Some considerations related to each of these possibilities are offered below.

Gastric emptying, i.e., the rate at which a substance leaves the stomach and enters the intestine (the primary absorptive site), is dependent upon the motility of the gastrointestinal tract. This motility, which is marked by phases, is distinctly different in fasted vs fed subjects. In dogs and in humans, the fasted state is characterized by cyclical intestinal motility and thus highly variable gastric emptying. Gastric emptying is slowest in phase I (quiescent phase), somewhat faster in phase II (intermittent contractile activity) and fastest in phase III (regular, strong contractions). This contractile activity cycles every two hours, with contractions propagating from the stomach down the intestine to the ileocecal region. For drugs with high membrane permeability, therefore, gastric emptying and drug absorption can be affected by changes in the length of the individual phases as well as the length of the cycle as a whole. In addition, tablets and capsules require contact between the dosage form and digestive fluids in order to disintegrate and dissolve. In microgravity, both the contact between the dosage form and the fluids, and the emptying of the combined substance through the pylorus, may be different than in 1-g.

The gastric emptying pattern in the fed state differs significantly from that of the fasted state, depending primarily on the number of calories in a meal. Liquid ingested with a meal empties relatively rapidly over 30 to 60 minutes. The solid component of the meal is broken down gradually through the mechanical action of contractions in the stomach combined with fluid, acid and enzyme secretions. Extensive studies in dogs indicate that

90% of the food particles leaving the stomach are less than 0.5 mm in size. Small particles (less than 1 mm) empty relatively rapidly with the liquid component of the meal, while larger spheres empty more slowly. Particles larger than 4 to 5 mm in diameter empty at the end of the meal, with the reappearance of phase III contractions marking the transition to the fasted-state motility pattern. Extensive studies in dogs and humans have indicated that particles of approximately 1.5 mm in diameter empty on the average at the same rate as the solid component of the meal. It is believed that this particle size is necessary to suspend a substance in fluid and to increase its surface area for efficient digestion.

Gastric emptying is dependent on particle size, particle density, and fluid viscosity. Simple fluid-mechanical considerations suggest that gastric emptying is determined by either the ratio of buoyancy force to drag force, or equivalently, the ratio of the Stokes settling velocity to mean fluid velocity. Consequently, gravity is intimately involved in controlling the emptying of particles from the stomach. There is a very high probability that gastric emptying in the fed state will be altered significantly in microgravity. The implications of these changes include not only changes in drug absorption but also changes in nutrient absorption and intestinal adaptation. For example, in a normal intestine, food is completely digested and absorbed by mid-gut. However, if food of a larger particle size empties from the stomach, digestion will take longer. It is well known that the intestine adapts to the presence of particular nutrients. Consequently, gastrointestinal motility in microgravity may slow via feedback from the intestine itself; the localized permeability of the intestinal membrane may also change.

In addition to drug absorption and portal-system availability, first-pass metabolism can significantly alter the systemic availability of active drugs. The absorption of some drugs such as propranolol and verapamil is dose-rate dependent. Furthermore, the isomer ratios of drugs can be dose-rate dependent if the individual isomers have different metabolic rate constants in the liver. Consequently, the systemic variability of an active drug can be affected by the input-rate dependence of liver metabolism. Consequently, the variability of a drug's plasma level associated with variable gastric emptying can be exaggerated through nonlinearity in metabolism. It is possible that the demonstrated variation in plasma levels of scopolamine and its varied effectiveness during space flight may be related to this mechanism.

Finally, the frequent occurrence of space motion sickness clearly alters gastrointestinal

function and drug absorption. Loss of appetite for several days or more also indicates significant alterations in gastrointestinal transit. While the mechanisms of these responses are not well understood, they provide additional evidence that gastrointestinal function is altered in microgravity. The duration of these changes should be studied in flight in order to determine the differences in gastrointestinal-tract function in microgravity compared to its function in 1-g, and to determine when the gastrointestinal tract adapts to microgravity.

Preliminary results clearly indicate that gastrointestinal functioning is significantly altered in space. This change in function will influence drug absorption through its effect on gastric emptying and intestinal transit as well as indirectly through the effects of dose rate on liver metabolism for drugs that exhibit nonlinear first-pass metabolism. Studies should be designed to measure gastric emptying and intestinal transit in both fasted and fed states in microgravity. Given the high degree of variability, studies should be conducted in the same individuals before flight, several times during flight, and after flight. Studies with drugs such as acetaminophen, aspirin and scopolamine as well as intestinal-transit markers such as lactulose may be used to measure the effects of gravity on both gastric emptying and intestinal transit. Such studies are not only fundamental to providing adequate drug therapy in space, but also may be valuable in designing appropriate types of nutrition in order to maintain high performance levels in microgravity.

Pharmacodynamic Aspects of Space Flight (Gerhard Levy)

The pharmacologic response to medications may be altered during and for some time following space flight and exposure to microgravity. This alteration would be expected to be quantitative rather than qualitative. It is likely to be caused by, or associated with, the pronounced physiologic changes that are being experienced during space flight, including those of cardiovascular function, neurovestibular performance, body water distribution, organ perfusion, and electrolyte concentrations. These changes may affect the pharmacokinetics as well as the pharmacodynamics of drugs. Pharmacokinetics pertains to the rates and rate constants of processes of drug absorption, distribution, metabolism and excretion, whereas the term pharmacodynamics, as used in this discussion, refers to the relationship between intensity of pharmacologic effects of medications and the concentrations of these medications and their active metabolites in the biophase (i.e., in the immediate environment of the site of action) or in fluids or tissues that reflect the biophasic concentrations.

Much is known about the processes that constitute the pharmacokinetic characteristics of drugs, including the molecular basis of xenobiotic transport and biotransformation. Conversely, much less is known about the mechanisms by which drugs elicit their desired and adverse pharmacologic effects. Particularly, post-receptor events that cause the ultimate expression of a ligand-recognition site interaction into clinically apparent effects remain to be fully elucidated. This limits severely our ability to predict the pharmacodynamic changes that may occur during space flight. On the positive side, however, it is likely that most if not all such changes will not be caused by microgravity per se, but by the physiologic perturbations that arise due to exposure to microgravity. These perturbations can be reproduced in a terrestrial setting, particularly in experimental animals but also to some degree in humans, and are therefore amenable to investigation under controlled conditions in normal laboratory or clinical environments.

The first principle in these studies, as well as in studies during space flight, is to make a clear distinction, both intellectually and practically, between pharmacokinetics and pharmacodynamics. Altered dose-response relationships may be due to altered

pharmacokinetic or pharmacodynamic characteristics, or both. Thus, the dose-response relationship is a hybrid, one that can lead to considerable confusion. It must be dissected into its dose-concentration and concentration-effect components.

Another important consideration, one that can account for considerable intra- as well as interindividual variation in the pharmacologic response to medications taken during space flight, is that the intensity of the pharmacologic response (effect) may be modified by stress, lack of sleep, changes in chronophysiologic status and other such factors in addition to the physiologic changes directly associated with microgravity. This implies the need for flexible drug dosage, inflight assessment of therapeutic response, and dosage titration based on that response.

Considering the fact that the physiologic perturbations due to microgravity do not arise instantaneously but develop over hours, days or weeks, it is to be expected that the effects of certain medications on crewmembers during space flight will change with time. It should be possible, however, at least in principle, to assess such time dependencies under experimental conditions on Earth. To the degree that medications will be taken by astronauts in space for experimental or therapeutic purposes, and that drug kinetics and/or dynamics will be measured under these conditions, it is highly desirable that they be preceded by and followed by at least one, preferably several, replications on Earth in order to assess intra-individual variation of parameter values. In view of the heavy work load of flight crews, and the presumed low priority and difficulty of performing meaningful pharmacokinetic-pharmacodynamic experiments on humans in space, serious thought should be given to in-flight animal experiments, with particular attention directed to the period immediately after flight, while alterations in physiologic status persist. Many of these studies can be performed on rodents, in conjunction with experiments under conditions of simulated weightlessness.

It is presumed that the crucial systemic medications for prolonged space missions (1 to 12 months) include antibiotics and other antiinfectives (including those for the urinary and gastrointestinal tracts), analgesics, antiarrhythmics and other drugs acting on the cardiovascular system (particularly on blood pressure), hypnotics, stimulants, steroids (as

both antiinflammatory and antistress agents), a histamine H₂-receptor antagonist, an antihistamine, an antiemetic, perhaps medication to prevent nephrolithiasis, and a blood volume expander. Of these agents, particular attention should be directed to drugs that act on the central nervous system, and therefore have the potential of affecting crew performance: hypnotics, stimulants, analgesics, antihistamines, and antiemetics such as scopolamine. It is necessary even on Earth to carefully titrate antiarrhythmic medication, so experimental investigations may be of limited predictive usefulness. Antibiotics are likely to present the fewest problems in terms of adverse effects (only a few antibiotics have potentially serious side effects) and efficacy (clinical concentrations are usually well above the minimum effective concentration).

It is recommended that initial studies be performed on rodents under conditions of simulated weightlessness. These studies should involve standard tests for CNS functionality such as rotarod, loss of righting-reflex activity, neurotoxicity (seizure threshold), maze performance, pain sensitivity (tail flick, electroshock) and analgesic response in association with drug concentration determinations. Test drugs for these initial studies should include an amphetamine, a barbiturate, a benzodiazepine, morphine, a nonnarcotic analgesic, scopolamine, cimetidine or ranitidine, and an antihistamine. Clinical studies in human volunteers during or after prolonged head-down bed rest can focus on the effect of these medications on hand-eye coordination, memory, arithmetic skill and other standard CNS performance tests.

Research Methodologies (Jerry Collins)

There are some special challenges for pharmacology studies in space. Yesterday, Stuart Feldman said our two goals were the search for new knowledge and for specific answers in order to treat individuals in specific situations. For modeling, we could restate the goals as individual-oriented or population-oriented. I would say that there are three distinct steps: The first, knowing the ground-based model that describes pharmacokinetics; the second, revising the model for space in light of mean values; and the third, individual modeling.

Computers play a role in all these steps. Micros, minis and mainframes can all work with all but the largest programs, since software has the dominant role. The two types of program applications are simulations and parameter estimation. In my experience, there are no universally accepted software packages, although several exist that have attractive features and are technically satisfactory. Simulation programs are less complex and less demanding than parameter estimation routines. Simulation programs, especially for physiologic pharmacokinetic models, allow the investigator to ask "What if...?" As Benet, Levy, and Wilkinson all noted yesterday, a straightforward approach would be to build a baseline physiologic model, then alter a parameter and find out what happens if cardiac output is redistributed. But, as noted yesterday, we do not have the database to decide how much to change the parameters. Also, although there are advantages to examining one critical variable, one should beware of over-simplified models that do not permit the investigator to see interactions among kinetic parameters.

Parameter estimation is fundamentally a process of collecting experimental data and plugging it into a computer program. However, no data should be entered into such a program without prior graphical analysis. Some data sets should never be subjected to computer analysis. If the graphical pattern is incompatible with the model assumptions, parameter estimation will be meaningless no matter how many digits are printed out.

Excellent programs are available to guide experimental design so as to minimize the number of samples per subject, a true constraint on most missions. NONMEM is one of these. However, these programs will not work well with the acetaminophen and

scopolamine data sets if ground-based models are used. Traditional model-definition studies must be done in the space environment for operationally significant drugs or model compounds. NONLIN, MLAB, SAAM, SIMUSDLV, and many other programs are quite adequate.

Finally, the link between kinetics and dynamics is always a key issue in pharmacologic studies, although this goal is often slighted, resulting in poor understanding of this link in many clinically used drugs. Experimental design is crucial in all cases, but especially when observations are limited. Continuous drug delivery systems greatly simplify this area and should be pursued. In particular, reevaluation of transdermal scopolamine should receive high priority.

SUMMARY AND RECOMMENDATIONS

The panel recommended that pharmacodynamic studies be conducted in four distinct but overlapping phases:

- Ground-based animal models (e.g., hindlimb-suspended rats)
- Ground-based 0-g simulation with human subjects (e.g., head-down bed rest)
- In-flight and postflight monitoring of pharmacological responses to well-characterized medication in animals
- Preflight, inflight, and postflight pharmacodynamic and clinical studies in humans

It was emphasized that because clearance, volume, half-life, and bioavailability all contribute to changes in pharmacokinetics, all should be evaluated. The following variables were identified as crucial to the understanding of pharmacokinetic and dynamic changes during flight: organ perfusion rates; hydration state and fluid distribution; renal function, as reflected by plasma protein and urine composition, volume and pH; blood pressure; drug-metabolizing enzyme activity; and circadian and diurnal variations. The magnitude of these and other physiological changes must be determined in order to determine whether they are large enough to affect mode of drug delivery. Furthermore, because physiological adaptation to microgravity is probably expressed differently in different crewmembers, intersubject variability must be taken into account during both ground-based flight simulation studies and in-flight studies.

Ground-based studies. The panel felt that identifying an appropriate ground-based model that reflects a number of microgravity-induced changes should be the immediate task. This model should be validated with drugs that will be used in flight. Such a model would be useful for the next 10 to 20 years. Information from ground-based studies, including steady-state animal data, can be used to derive physiological models; however, parameters to be modeled must be selected carefully. The pharmacokinetic computer programs NONLIN, NONMEM, ADAP, or other programs can be used for data analysis on mainframes or on PCs. Identifying spaceflight-related changes in plasma-to-tissue partitioning coefficients, distribution, and excretion can be accomplished using animal models. Salivary flow dynamics and composition should be evaluated in order to validate

the saliva sampling method in space.

In-flight studies. In order to assess the pharmacodynamic consequences of microgravity, data on drug action vs. drug concentration must be collected during flight. Investigators must collaborate in designing sample collection strategies, so that the limited opportunities for collecting in-flight data can be useful to the greatest number of investigators. Collecting medical information from previous US and Soviet flights is strongly recommended in order to better understand the behavior of some of the medications administered during flight.

Drug selection. Concerning the selection of drugs for study, the panel recommended studying first those drugs with a narrow therapeutic index that are likely to be used in flight, such as some cardiovascular drugs. Microgravity-induced changes in the absorption and metabolism of such drugs would pose the greatest risk to crewmembers during flight. The protein-binding characteristics of these drugs should be thoroughly characterized, and data collected after landing as well as during flight. Procedurally, it was suggested that Phase I to Phase IV IND protocols be developed for drugs that are to be used by crewmembers during flight. During discussions of specific drugs, the point was raised that absorption and metabolism of acetaminophen reflects the functioning of but a single enzyme system; other enzyme systems should also be evaluated. Bed rest can be used to evaluate changes in rapidly cleared drugs such as lidocaine. Antipyrine was proposed as a test compound that can illustrate fluid distribution patterns as well as metabolic function. It was suggested that multiple doses of stable labeled compounds could be used to monitor drug metabolism and distribution during flight. The general consensus of the panel concerning selection of drugs for study in flight was to use those drugs with a wide therapeutic margin whenever they are available, so that unforeseen therapeutic consequences due to flight-induced physiological changes can be avoided.

Dosage forms. Liquid dosage was considered the best form for in-flight drug delivery; however, it was acknowledged that motion sickness may interfere with the effectiveness of oral administration. Other potential dosage forms include oral strips or granules; suppositories; nasal drops or sprays; transdermal unit-dose delivery systems; and

intramuscular injections. These forms should be tested during bed rest before implementation during flight.

Finally, the panel recommended addressing the following research questions: (1) differentiating intrinsic vs. flow-limited changes in liver metabolism during space flight; (2) determining hepatic extraction as a function of perfusion, oxygenation and hematocrit; and (3) determining the effect of glomerular filtration rate on rate of excretion. These factors must be evaluated on a drug by drug basis, using drugs with a narrow therapeutic index.



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16. Abstract The Pharmacokinetics and Pharmacodynamics Panel met on August 29-30, 1988 at the Lunar and Planetary Institute in Houston, Texas to discuss pharmacokinetic and pharmacodynamic implications of space flight and make recommendations for operational and research strategies. Based on the knowledge available on the physiological changes that occur during space flight, the dependence of pharmacokinetics on physiological factors, and the therapeutic requirements for future space missions, the panel made several recommendations for research. It was suggested that using medications available with a large (wide) therapeutic window will avoid unforeseen therapeutic consequences during flight. The sequence for conducting research was outlined as: 1. Identify ground-based simulation models (e.g., antiorthostatic bedrest) for conducting pharmacokinetic and pharmacodynamic research; 2. Estimate parametric changes in these models using pharmacologic agents that have different pharmacokinetic characteristics and a narrow therapeutic index; 3. Verify these findings during flight; and 4. Develop and identify appropriate and effective drug delivery systems, dosage forms and regimens. The panel recommended gaining a thorough understanding of the pharmacokinetic deviations of medications that have a narrow therapeutic index (e.g. cardiovascular drugs and sedative hypnotics) in order to ensure safe and effective treatment during flight with these agents. It was also suggested that basic information on physiological factors such as organ blood flow, protein composition and binding, tissue distribution, and metabolism by hepatic enzymes must be accumulated by conducting ground-based animal and human studies using models of weightlessness. This information will be useful to construct and identify physiologically based pharmacokinetic models that can provide valuable information on the pharmacodynamic consequences of space flight and aid in identifying appropriate therapeutic regimens.					
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